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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,298	12/18/2006	M. Ian Phillips	USF-200TCXZ1	6761

23557 7590 02/08/2010

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
02/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,298	PHILLIPS ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-20 and 28-34* is/are pending in the application.

4a) Of the above claim(s) *15 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,16-19 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/22/2010 has been entered.

This application 10/567,298 is a 371 of PCT/US04/26195 filed on 08/11/2004 which claims benefit of 60/494,184 filed on 08/11/2003, and claims benefit of 60/494,185 filed on 08/11/2003, and claims benefit of 60/513,067 filed on 10/21/2003, and claims benefit of 60/513,657 filed on 10/23/2003.

Election/Restriction

Claims 14 and 21-27 are cancelled. Claim 15 is amended. Claims 1-13, 15-20 and 28-34 are pending.

It is noted that claim 15 filed on 01/22/2010 has been amended to recite "wherein said therapeutic products are different" instead of previously recited limitation "wherein said therapeutic products are the same or different". In this regard, it is worth noting that Applicants elected heme oxygenase-1 (HO-1) as the single therapeutic product from claim 7 (See page 2 of office action mailed on 02/04/2009). Therefore, the limitation "wherein said therapeutic products are different" recited in amended claim 15 is considered as non-elected species

Accordingly, claims 15 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1-13, 16-19, and 28-34 are currently under examination to the extent of elected species, as documented on pages 2-4 of the office action mailed on 07/22/2009, which are (i) mesenchymal stem cell (MSC), which has the capacity to differentiate into a cardiac cell, with respect to a genetically modified stem or progenitor cell, and (ii) heme oxygenase-1 (HO-1) gene with respect to a nucleic acid sequence encoding a therapeutic product, and (iii) hypoxia with respect to a physiological stimulus.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Previous rejection of claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***moot*** because the claim has been cancelled.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-9, 11-13, 16-19, and 28-34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. *J Gene Med.* 3(3):240-51, 2001) and **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25, 2001). Applicant's arguments filed 01/22/2010 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-16 of the office action mailed on 07/22/2009.

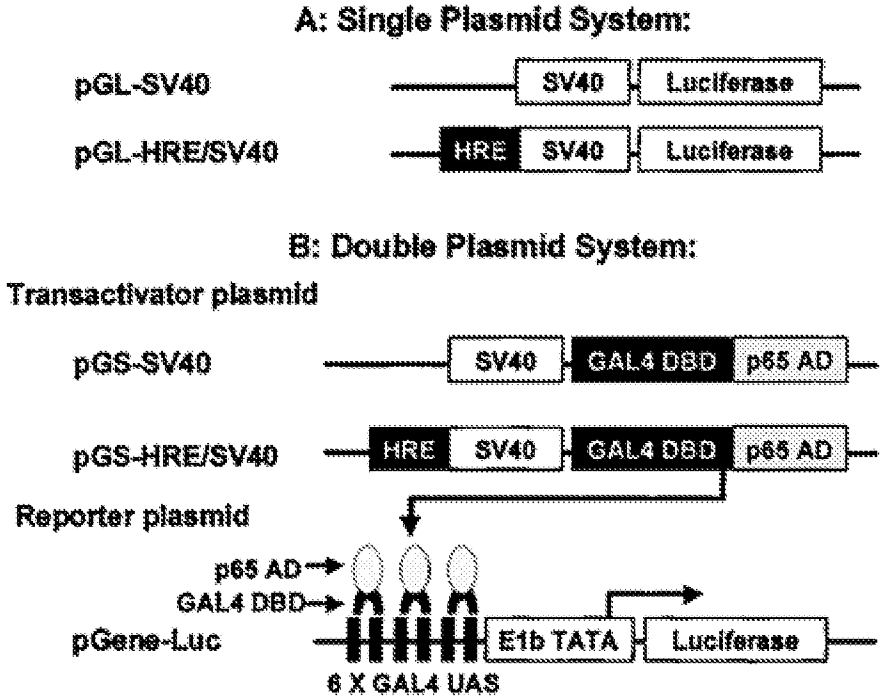
Claim 1 filed on 01/22/2010 reads as follows: A genetically modified stem or progenitor cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

Claim 28 filed on 01/22/2010 reads as follows: A modified mammalian tissue, wherein said tissue comprises a genetically modified mammalian stem or progenitor cell, wherein said cell comprises: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

Claim interpretation: The limitation "wherein said therapeutic product is a polypeptide that is endogenous to said cell" recited in claim 17 is interpreted as any therapeutic product that is a polypeptide encoded by a transgene (i.e. exogenous polynucleotide) and the genome of said cell comprises gene(s) on chromosomes that can encode the same polypeptide (which is considered endogenous to the said cell). The limitation "A modified mammalian tissue" recited in claim 28 reads on (i) a mammalian tissue differentiated from the recited genetically modified mammalian stem cell, and (ii) a mammalian tissue comprises the recited genetically modified mammalian stem cell, which is transplanted to an existing mammalian tissue.

With regard to the limitations of claims 1-6, 8, 11, 12, 16-19, and 28-34 of instant application, Tang et al. teaches that coronary artery disease frequently involves repeated bouts of myocardial ischemia (which reads on hypoxia recited in claims 18, 19, and 33), and to automatically up-regulate the cardioprotective transgenes under hypoxic ischemia, a "vigilant vector" gene therapy system was developed and tested in a rat embryonic cardiac myoblast (H9c2). Tang et al. teaches that, in the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal. Furthermore, Tang et al. teaches that a novel double plasmid system was designed to elevate the potency of the vigilant vector, and instead of putting the promoter and the reporter gene in the same plasmid (single plasmid system), Tang et al. separated them into two plasmids: the transactivator plasmid and reporter plasmid (double plasmid system). Tang teaches that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain (which reads on the limitations of claim 6 of instant application), and the chimeric regulator binds specifically to the

upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene (See abstract and Figure 1 shown below, Tang et al., 2002).



Tang et al. does not explicitly teach **(I)** a genetically modified stem cell recited in claim 1 and a mesenchymal stem cell (MSC) recited in claims 13 and 34, and **(II)** a nucleic acid sequence encoding a therapeutic product recited in claim 1 and said therapeutic product being heme oxygenase-1 (OH-1) recited in claim 7 and adenovirus recited in claim 9 of instant application, and **(III)** a modified mammalian tissue recited in claim 28 and its dependent claims 29-33.

(I) Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types. Turgeman et al. teaches that hMSCs represent a novel platform for skeletal gene therapy and that hMSCs can be genetically

engineered to express desired therapeutic proteins inducing specific differentiation pathways (See abstract, page 240, Turgeman et al.).

(II) Juan et al. teaches the followings: (i) adenovirus-mediated gene transfer of HO-1 (which reads on claims 9 and 32 of instant application) in arteries reduces iron overload and inhibits lesion formation in apolipoprotein E (apoE)-deficient mice (See abstract, Juan et al., 2001), and (ii) heme oxygenase (HO) is a rate-limiting enzyme in heme catabolism; one of the isozymes, HO-1, is a stress-response protein and can be induced by a variety of oxidation-inducing agents, including heme/hemoglobin, heavy metals, UV radiation, cytokines, and others, and induction of HO-1 leads to the degradation of pro-oxidant heme to carbon monoxide (CO) and biliverdin (See introduction, page 1519, Juan et al., 2001).

(III) With regard to the limitation "a modified mammalian tissue" recited in claim 28, the limitation "a human cell" recited in claim 29, the limitation "said cell is autologous to said tissue" recited in claim 30, and the limitation "mesenchymal tissue" recited in claim 31, Turgeman et al. teaches that genetically engineered hMSCs displayed enhanced proliferation and osteogenic differentiation in culture; *in vivo*, transplanted genetically engineered hMSCs were able to engraft and form bone and cartilage in ectopic sites, and regenerate bone defects (non-union fractures) in mice radius bone; and importantly, the same results were obtained with hMSCs isolated from a patient suffering from osteoporosis (See abstract and Figure 4, Turgeman et al., 2001). It is noted that the formation of new bone and cartilage in ectopic sites comprising cells differentiated from hMSCs taught by Turgeman et al. (2001) reads on the limitation "mesenchymal tissue" recited in claim 31, and the limitation "said cell is autologous/syngenic to said tissue" recited in claim 30.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of (i) Tang et al. regarding a genetically modified/transfected cell comprises two plasmids: the transactivator plasmid and reporter plasmid and that that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain, and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene, with the teachings of (ii) Turgeman et al. regarding the use genetically engineered hMSCs for gene therapy to express desired therapeutic proteins, whereas the hMSCs can be directed to specific differentiation pathways to form mesenchymal tissue, and the teachings of (iii) Juan et al. regarding expressing HO-1 gene from an adenoviral vector for therapeutic purpose, to arrive at the claimed genetically modified stem cell comprising expression cassette as recited in claims 1-9, 11-13, 16-19, and 28-34 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Tang et al., Turgeman et al., and Juan et al. because (i) Tang et al. establishes the double plasmid system sensitive to hypoxia condition for gene therapy of coronary artery disease by monitoring the expression of luciferase as a reporter, (ii) Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types and hMSCs can function as a transgene vehicle and can be genetically engineered to express desired therapeutic proteins and the genetically engineered hMSCs can be induced toward specific differentiation pathways to form mesenchymal tissue for treatment, and

(iii) Juan et al. teaches Adv-OH-1 construct (which expresses OH-1 from an adenoviral vector) for gene therapy of atherosclerosis since HO-1 is a stress-response protein and can be induced by a variety of oxidation-inducing agents. Furthermore, substitution of a reporter gene with a gene encoding a therapeutic protein in the context of a vector, either a plasmid or a viral vector, is a common practice in molecular biology depending on the gene of interest to be expressed.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoblast cell line by the teachings of Tang et al., (ii) demonstration of genetically engineered human mesenchymal stem cells expressing human BMP-2 from an adenoviral vector leading to formation of cartilage and bone *in vivo* for treatment of osteoporesis by the teachings of Turgeman et al., and (iii) the transfection and expression of Adv-OH-1 construct for gene therapy of atherosclerosis by the teachings of Juan et al., and

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that Tang et al. reference does not teach or suggest the use of stem or progenitor cells, and more particularly, does not teach or suggest the use of cells autologous to the tissue. Applicant argues that the vector described in the Tang et al. reference was designed specifically for injection directly into heart tissue and not for use in stem cells. Thus, a person of ordinary skill in the art would not look to incorporate the vector of the Tang et al. reference into a stem cell or progenitor cell. Applicant states that the secondary references cited by the Examiner under these rejections also do not provide any motivation to genetically modify a stem or progenitor cell with a first and second polynucleotide having the elements as recited in the claims.

Applicants maintain the position that the combination of a gene switch/biosensor and a gene amplification system in a stem cell or a progenitor cell is novel and not obvious over the teachings of the cited references. Applicants' claimed invention advantageously provides for cell therapy wherein a patient can have their own stem or progenitor cells prepared from their own tissue (e.g., bone marrow) and then the cells can be provided with a vector (e.g., hypoxia gene switch/transgene) outside the body before injecting the modified cells directly into the target tissue (e.g., heart) of the patient. Applicant argues that the claimed invention provides cells, such as adult stem cells derived from bone marrow, a novel and surprising means of surviving in a hostile environment (such as in an injured heart where oxygen levels are very low). It was not obvious to provide cells with means for surviving in the hostile environment because the high rate of death of implanted stem cells was not known in the art at the time of the present invention. Applicant states that when bone marrow stem cells are transplanted into ischemic hearts, the majority of the engrafted cells (over 90%) die within 1-2 days. It is only the present invention that solved the problem of poor cell survival that occurs in stem cell therapy. Applicant states that none of the cited references teach or suggest anything of relevance in regard to the problem of implanted stem cell survival and, thus, a person of ordinary skill in the art would not have been motivated to combine the exogenous first and second polynucleotide of the subject invention into a stem cell or a progenitor cell. Applicant argues that in order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation for combining the references. In re Geiger, 2 USPQ2d 1276 (Fed. Cir. 1987). The fact that the high rate of death of implanted stem cells was not known in the art at the time of the subject invention is evidence as to the nonobviousness of the claimed invention.

Applicant states that the Tang et al. reference describes testing different types of gene switches, including single vector and double vector models. The rat myoblast cell line H9c2 referred to in the Tang et al. reference was only used for testing the vector. It was not used for stem cell transplantation. Nowhere in the Tang et al. reference did the authors teach or suggest an approach for improving stem cell survival in therapy. The work reported in the Tang et al. reference is directed solely to development of an injectable gene switch which would reside in specific body tissue, such as heart ventricle, defined by the promoter incorporated into the gene

switch. Thus, a person of ordinary skill in the art would not have looked to the Tang et al. reference for teachings relevant to the preparation of Applicants' claimed invention.

Applicants maintain the position that the cited references do not teach or suggest a mammalian tissue comprising a genetically modified mammalian stem or progenitor cell as claimed in new claims 28-34. There is no teaching or suggestion in any of the cited references to provide mammalian tissue with a genetically modified stem cell or progenitor cell of the invention. As noted above, the Tang et al. reference is concerned with direct gene therapy and not with cell therapy. Thus, Tang et al. is only relevant with regard to transforming cells within a tissue with nucleic acid vector. Applicant states that, as noted previously, the intended use of the genetically modified stem cell or progenitor cell is discussed to point out why a person of ordinary skill in the art would not look to the teachings of the cited references, i.e., because they are directed to uses that are not relevant to the claimed invention. It was only the inventors of the claimed invention that realized the problem to be solved and did so by invention of the claimed genetically modified stem cell or progenitor cell and mammalian tissue.

Applicants maintain the position that the secondary references, Juan et al., Nicklin et al., and Turgeman et al., cited under the §103 rejections fail to cure or overcome the deficiencies of Tang et al., the primary reference. The Juan et al. reference is irrelevant as it does not teach or suggest that heme oxygenase 1 is cell protective against apoptosis. Thus, an ordinarily skilled artisan would not have looked to use a polynucleotide encoding heme oxygenase 1 in a genetically modified stem or progenitor cell of the claimed invention.

Response to Applicant's arguments

In response to applicant's arguments against the references individually, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments the vector described in the Tang et al. reference was designed specifically for injection directly into heart tissue and not for use in stem cells, and a person of

ordinary skill in the art would not look to incorporate the vector of the Tang et al. reference into a stem cell or progenitor cell, have been fully considered and found not persuasive. The Examiner notes that the there is nothing taught by Tang et al. indicates that the plasmids expressed in the embryonic cardiac myoblast cell line H9c2 are myoblast specific and cannot be expressed in the mesenchymal stem cells (MSCs) taught by Turgeman et al. Furthermore, Turgeman et al. specifically teaches human MSCs as a platform for skeletal cell mediated gene therapy. A skilled artisan will certainly appreciate the differentiation potential of mesenchymal stem cells taught by Turgeman et al. as advantageous when compared to fully differentiated cardiac myoblast cell line H9c2 taught by Tang et al. in the context of cell mediated gene therapy for damaged ischemic heart tissue.

Applicant's arguments that "the claimed invention provides cells, such as adult stem cells derived from bone marrow, a novel and surprising means of surviving in a hostile environment (such as in an injured heart where oxygen levels are very low), and it was not obvious to provide cells with means for surviving in the hostile environment because the high rate of death of implanted stem cells was not known in the art at the time of the present invention" have been fully considered and found not persuasive. *It should be emphasized that "surviving in a hostile environment (such as in an injured heart where oxygen levels are very low)" is taught by primary reference Tang et al.,* not by Turgeman et al. As responded in the preceding paragraph, Turgeman et al. specifically teaches human MSCs as a platform for skeletal cell mediated gene therapy. A skilled artisan will certainly appreciate the differentiation potential of stem cells taught by Turgeman et al. as advantageous when compared to fully differentiated cardiac myoblast cell line H9c2 taught by Tang et al. in the context of cell mediated gene therapy for damaged ischemic heart tissue. Furthermore, relevant to Applicant's arguments pertaining to feasibility of stem cell therapy, it is worth noting that isolation of a cardiomyogenic cell line (CMG cell) from murine bone marrow mesenchymal stem cells and cell transplantation therapy for the patients with heart failure might be achieved using the regenerated cardiomyocytes from autologous bone marrow cells was known in the art before the claimed priority date of instant application (See for instance, **Fukuda et al.,** Regeneration of cardiomyocytes from bone

marrow: Use of mesenchymal stem cell for cardiovascular tissue engineering, *Cytotechnology* 41(2-3):165-75, 2003).

With regard to Applicant's arguments that nowhere in the Tang et al. reference did the authors teach or suggest an approach for improving stem cell survival in therapy, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf) (citing KSR, 82 USPQ2d at 1936). The Examiner also notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine The Tang et al. (2002), Turgeman et al. (2001), and Juan et al. (2001) has been clearly set forth on pages 10-11 of the Non-Final office action mailed on 02/04/2009, and reiterated in this office action with editorial revisions.

Applicant's arguments that "Tang et al. is only relevant with regard to transforming cells within a tissue with nucleic acid vector, and the intended use of the genetically modified stem cell or progenitor cell is discussed to point out why a person of ordinary skill in the art would not look to the teachings of the cited references, i.e., because they are directed to uses that are not relevant to the claimed invention" have been fully considered and found not persuasive. Applicant's arguments appear to arbitrarily divide skilled artisan into mutually exclusive group of "gene therapy" and group of "cell therapy", and skill artisan of "gene therapy" will never read the literature published by skill artisan of "cell therapy" because they are irrelevant. This is certainly not true because Turgeman et al. clearly indicate "gene therapy" can be mediated through cells transfected with desired gene (See title of Turgeman et al. --- Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy).

As discussed and responded in preceding paragraphs, the intended use of claimed products (a genetically modified stem cell comprising recited plasmids) would have been a reasonable expectation of success in term of stem cell mediated gene therapy by combined teachings of Tang et al., Turgeman et al., and Juan et al. *Furthermore, the Examiner maintains*

the position that intended use of claimed products bears limited, if any patentable weight. The structure and inherited characteristics of claimed products as a whole is clearly *prima facie* obvious based on the combined teachings of Tang et al., Turgeman et al., and Juan et al.

3. Claim 10 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. *J Gene Med.* 3(3):240-51, 2001) and **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25,2001), as applied to claims 1-9, 11-13, 16-19, and 28-34 above, and further in view of **Nicklin et al.** (Nicklin et al., Tropism-modified adenoviral and adeno-associated viral vectors for gene therapy, *Curr Gene Ther.* 2(3):273-93, 2002). Applicant's arguments filed 01/22/2010 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 16-18 of the office action mailed on 07/22/2009.

The teachings of Tang et al., Turgeman et al., and Juan et al. have been discussed in the preceding section of the rejection of claims 1-9, 11-13, 16-19 and 28-34 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. in view of Turgeman et al. and Juan et al.

None of Tang et al., Turgeman et al., and Juan et al. teaches adeno-associated virus as a vector recited in claim 10.

Nicklin et al. et al. teaches that advances in vector targeting strategies have been rapid within the field of DNA-based viruses, particularly adenovirus (Ad) and more recently adeno-associated virus (AAV) based vectors, and both Ad and AAV vectors can be modified in tropism for gene therapy purpose.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to integrate the teachings of Nicklin et al., regarding use of adeno-associated virus (AAV) based vectors in gene therapy with the combined teachings of Tang et al., Turgeman et al., and Juan et al. regarding expressing a therapeutic gene from an adenoviral vector in a genetically modified mesenchymal stem cell, by substituting adenoviral vector taught by Juan et al. with an adeno-associated vector taught by Nicklin et al. to arrive at the claim 10 of instant application.

One having ordinary skill in the art would have been motivated to integrate the teachings of Nicklin et al. with the combined teachings of Tang et al., Turgeman et al., and Juan et al. because Nicklin et al teaches that both adenovirus (Ad) and adeno-associated virus (AAV) based vectors can be modified in tropism for gene therapy purpose.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoblast cell line by the teachings of Tang et al., (ii) demonstration of genetically engineered human mesenchymal stem cells expressing human BMP-2 from an adenoviral vector leading to formation of cartilage and bone *in vivo* for treatment of osteoporesis by the teachings of Turgeman et al., (iii) the transfection and expression of Adv-OH-1 construct for gene therapy of atherosclerosis by the teachings of Juan et al., and (iv) demonstration of both

adenovirus (Ad) and adeno-associated virus (AAV) based vectors can be modified in tropism for gene therapy purpose by the teachings of Nicklin et al. et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and response to Applicant's arguments are the same as documented in the rejection claims 1-9, 11-13, 16-19, and 28-34 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (2002) in view of Turgeman et al. (2001) and Juan et al. (2001) in this office action.

Conclusion

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
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